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Chapter “Stress : Definition and History”

Stress: Definition and History

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Introduction and Historical Outline of Several Stress Concepts

Aristotle, Hippocrates, and the other Ancients were aware of stress and its adverse effects. However, Claude Bernard was the first to formally explain how cells and tissues in multicelled organisms might be protected from stress. One of the world's greatest physiologists, Bernard, working in Paris during the second half of the nineteenth century, first pointed out (1859) that the internal medium of the living organism is not merely a vehicle for carrying nourishment to cells. Rather, “it is the fixity of the milieu intérieur which is the condition of free and independent life.” That is, cells are surrounded by an internal medium that buffers changes in acid-base, gaseous (O₂ and CO₂), and ion concentrations and other biochemical modalities to minimize changes around biologically determined set points, thereby providing a steady state. Fifty years later, Walter Bradford Cannon, working at Harvard, suggested the designation **homeostasis** (from the Greek *homoios*, or similar, and *stasis*, or position) for the coordinated physiological processes that maintain most of the steady states in the organism. Cannon popularized the concept of ‘homeostasis’ in his 1932 book, *Wisdom of the Body*.

Cannon also coined the term **fight or flight** to describe an animal's response to threat. The concept of fight or flight proposes that animals react to threats with a general discharge of the sympathetic nervous system, priming the animal for fighting or fleeing. This response was later recognized as the first stage (acute stress response) of a **general adaptation syndrome (GAS)** postulated by Hans Selye to be a universal stress response among vertebrates and other organisms.

Born in Vienna in 1907, Hans Hugo Bruno Selye, also known as the ‘father of stress,’ began his stress research while still a medical student in 1926. He observed that patients with a variety of illnesses had many of the same ‘nonspecific’ symptoms that were a common response to stressful stimuli experienced by the body. These clinical observations together with experiments on laboratory rats underpinned Selye's concept of GAS, which led Selye to assert that prolonged exposure to stress resulted in ‘**diseases of adaptation**.’ That is, chronic stress, by causing the overproduction of chemicals and hormones, produced gastroduodenal ulcers and high blood pressure. Although the GAS hypothesis was subsequently shown to be incorrect, it did put stress on the map and also highlighted the fact that stress had major effects on the immune system as well as on the adrenal glands.

In addition to providing the first clear definition of stress, Hans Selye was also the first to recognize that homeostasis could not by itself ensure stability of body systems under stress. He coined the term **heterostasis** (from the Greek *heteros*, or other) as the process by which a new steady state was achieved by treatment with agents that stimulate the physiological adaptive

mechanisms. Heterostasis could be regarded as the precursor for the concept of **allostasis**, first advanced by Peter Sterling and Joseph Eyer in the 1980s. That is, homeostasis, which has dominated physiological and medical thinking since the nineteenth century, is thought to provide 'stability through constancy.' Allostasis, on the other hand, provides 'stability through change' brought about by central nervous regulation of the set points that adjust physiological parameters to meet the stress/challenge.

A different tack, focused on cognition, was taken by Richard Lazarus, the eminent and influential Berkeley University psychologist. At a time when psychology tried to understand human behavior by first understanding simple organisms engaging in simple behaviors learned by associations, rewards, or punishments, Lazarus instead emphasized the importance of studying cognition, which he extended into stress and coping.

Epidemiology has been and remains central to stress studies. Numerous epidemiological studies have tried to define the effects of social, workplace, and lifestyle on stress, health, and well-being. However, of the recent epidemiological studies that have generated new stress concepts, the most important perhaps is that of David Barker, which led to the hypothesis that **fetal undernutrition in middle to late gestation programs later coronary heart disease**. This concept was soon extended by Hales and Barker in their '**thrifty phenotype hypothesis**.' The latter proposes an association between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome, which afflict communities in epidemic proportions. Poor nutrition in early life, it is postulated, produces permanent changes in glucose-insulin metabolism. These changes include insulin resistance (and possibly defective insulin secretion), which combined with effects of obesity, aging, and physical inactivity are the most important factors in determining type 2 diabetes. Many studies worldwide have confirmed Barker's initial epidemiological evidence, although the strength of the relationships has varied between studies.

With advances in genomics, the concept of susceptibility genes that increase the vulnerability of individuals to stressful life events has attracted considerable research interest. Thus, for example, the work of Avshalom Caspi and associates suggests that a polymorphism in the monoamine oxidase A (MAOA) gene promoter, which reduces MAOA expression, influences vulnerability to environmental stress, and that this biological process can be initiated by childhood abuse. Furthermore, Caspi and associates, working at the Institute of Psychiatry, London, have demonstrated that a polymorphism in the promoter of the serotonin transporter gene can render individuals more susceptible to stressful life events. In addition to their disorder-specific value, these findings have heuristic value for further thinking and research on genetic-environmental interactions that determine the response to stress and the development of mental disorders.

In parallel with these stress concepts, neuroendocrine advances revealed the physiological substrate for homeostasis, allostasis, and the stress response mechanisms. The autonomic nervous and the hypothalamic–pituitary–adrenocortical (HPA) systems subserve the afferent and efferent limbs of the stress response in vertebrates and are also central to maintaining homeostasis and effecting allostasis. The term autonomic nervous system was coined in 1898 by the Cambridge physiologist John Newport Langley, who was also renowned for his development (in parallel with Paul Ehrlich) of receptor theory. Controlled by the brain, and utilizing as neurotransmitters epinephrine and norepinephrine (sympathetic nervous component) or acetylcholine (parasympathetic component), the role of the autonomic nervous

system in fight-or-flight and homeostasis (especially cardiovascular) was clearly explained by Walter Cannon.

The story of our understanding of the HPA, and the concept of the neurohumoral hypothesis of anterior pituitary control, is tortuous. The pituitary gland had long been regarded, by luminaries such as the great Harvard neurosurgeon Harvey Cushing, as the autonomous controller of the adrenal cortex, the thyroid, and the gonads. That is, the anterior pituitary gland was considered to be the 'conductor of the endocrine orchestra.' This view was reinforced by the dramatic effects of experimental pituitary removal (hypophysectomy) in rodents made feasible by the parapharyngeal surgical approach to the pituitary developed by PE Smith in approximately 1930. However, at approximately the same time, experiments were in progress that would eventually prove that the anterior pituitary gland is not autonomous; rather, it is controlled by the brain. The first of these experiments, carried out by William Rowan working alone at -50 °C in Edmonton, Alberta, in the late 1920s, showed that migration in birds was controlled by the gonads, and that gonadal size in birds was increased many-fold by increases in day length. Day length and the effects of other exteroceptive factors, such as stress, on endocrine function together with the effects of brain tumors and trauma in the human led to an acceptance of the then (1930s) revolutionary concept that the pituitary gland is under central nervous system (CNS) control.

The neural lobe of the pituitary gland is composed of nerve projections from the paraventricular and supraoptic nuclei of the hypothalamus: these projections terminate on systemic blood vessels into which they release the nanopeptide neurohormones, vasopressin and oxytocin. In contrast, the anterior pituitary gland receives no direct innervation from the brain. Rather, the CNS control of the anterior pituitary gland is mediated by neurohormones synthesized and released from hypothalamic neurons and transported to the anterior pituitary gland by the hypophysial portal vessels. Proof of the neurohumoral hypothesis of anterior pituitary control came, first, from the elegant pituitary stalk section and pituitary grafting experiments of Geoffrey Harris and Dora Jacobsohn; second, from the characterization of some of the neurohormones by Andrew Schally and Roger Guillemin, for which they were awarded the 1977 Nobel Prize for physiology and medicine; and third, from the demonstration, first by my group, that these neurohormones were indeed released into hypophysial portal blood. Corticotropin-releasing factor (CRF), a 41-amino-acid peptide that mediates neural control of adrenocorticotrophic hormone (ACTH) release from pituitary corticotropes, was isolated and sequenced by Wylie Vale and associates in 1981. A series of physiological studies, including measurements of neurohormone release into hypophysial portal blood in vivo, have confirmed earlier views that arginine vasopressin acts synergistically with CRF to control ACTH release.

Finally, no outline of the history of stress concepts would be complete without mention of the characterization of the adrenocortical glucocorticoids and their function. The glucocorticoids are steroid hormones whose secretion by the adrenal cortex is controlled by ACTH. The hormones of the adrenal cortex were isolated, identified, and synthesized independently by Edward Kendall (at the Mayo Foundation) and Tadeus Reichstein (at Zurich) and their associates. The availability of large amounts of synthetic steroids enabled their physiological effects to be studied. Ultimately, Philip Hench was able to test the glucocorticoid, cortisone, in the human and demonstrate that it is a powerful anti-inflammatory agent. Hench, at the Mayo Foundation, had previously observed that rheumatoid arthritis was sometimes relieved during pregnancy and in some patients with jaundice, leading him to conclude that the pain-alleviating substance was a steroid. Kendall, Hench, and Reichstein were jointly awarded the Nobel Prize for

physiology and medicine for 1950, and synthetic glucocorticoids continue to be used to treat arthritis, asthma, autoimmune conditions, and other inflammatory disorders in humans.

Definitions of Stress

Stress has a different meaning for different people under different conditions. The first and most generic definition of stress is that proposed by Hans Selye: “Stress is the nonspecific response of the body to any demand.” Selye repeatedly emphasized the fact that the continued use of the word stress as a nonspecific response to any demand was most appropriate. Selye argued that stress is not identical to emotional arousal or nervous tension since stress can occur under or in response to anesthesia in man and animals, and it can also occur in plants and bacteria that have no nervous system. This point is elaborated later in the context of stress-induced heat shock proteins (Hsps) that play a key role in cytoprotection across all three phylogenetic domains of organisms on Earth. The word stress, as used by Selye, is accepted in all foreign languages, including those in which no such word existed previously.

Stress, Selye underscored, is not something to be avoided. Indeed, it cannot be avoided, since just staying alive creates some demand for life-maintaining energy. Even when man is asleep, his heart, respiratory apparatus, digestive tract, nervous system, and other organs must continue to function. Complete freedom from stress can be expected only after death.

There has been much controversy and debate about Selye’s concepts and particularly Selye’s view that stress is best regarded as a nonspecific response. Because of their heuristic value, these points will be further considered later.

Other definitions, reviewed in detail by Selye in his treatise *Stress in Health and Disease*, include the following:

1. In behavioral sciences, stress is regarded as the “perception of threat, with resulting anxiety discomfort, emotional tension, and difficulty in adjustment.”
2. In the group situation, lack of structure or loss of anchor “makes it difficult or impossible for the group to cope with the requirements of the situation, and the problem of leadership and interpersonal behavior becomes one of evolving or supplying a structure or anchor and of supplying the expertness for coping with the demands of the situation.”
3. Stress can also be defined in terms of pure neuroendocrinology. Eugene Yates, for example, defined stress as any stimulus that will provoke the release of ACTH and adrenal glucocorticoids. Presumably, the same might apply to the equally powerful sympathetic markers of stress, underscored earlier by Walter Cannon.
4. Finally, Selye also mentions Richard Lazarus, famous for his work in cognitive psychology and focus on the emotions. Lazarus underscores the difficulties of reaching a precise overarching definition of stress by setting out the following different meanings of the term:
“In spite of consistent confusion about the precise meaning of the term, stress is widely recognized as a central problem in human life. Scientists of many disciplines have conceptualized stress but each field appears to have something different in mind concerning its meaning. For the sociologist, it is social disequilibrium, that is, disturbances in the social structure within which people live. Engineers conceive of stress as some external force which produces strain in the materials exposed to it. Physiologists deal with the physical stressors that include a wide range of stimulus conditions that are noxious to the body. In the history of psychological stress research, there has been no clear separation between physical stressors which attack biological

tissue systems and psychological stressors which produce their effects purely because of their psychological significance.”

Selye’s Definition of Stress – A Further Consideration

Selye’s definition and concept of stress has remained controversial. For some, his definition is too biological and ignores cognitive and psychological factors, a criticism that seems to stem from the mistaken idea that cognition is not a function of the brain (a reversion to Rene Descartes’ outmoded doctrine that mind and body are separate). For others, Selye’s definition is too general. This section reviews the basis for Selye’s definition of stress and considers whether the criticisms leveled at Selye’s stress concept are valid. Overall, our observations suggest that Selye fully understood so-called psychological or cognitive stress, and that the generality of Selye’s stress definition has facilitated the molecular, genotypic, and phenotypic analysis of stress and stress responses across all species from bacteria to man.

General Adaptation Syndrome

Selye first put stress on the map with GAS. In search of a new hormone, Selye injected extracts of cattle ovaries into rats. The injection caused the following characteristic triad:

1. The adrenal cortex became enlarged and discharged lipid secretory granules.
2. The thymus, spleen, lymph nodes, and all other lymphatic structures showed severe involution.
3. Deep bleeding ulcers appeared in the stomach and duodenum.

Selye at first thought that these effects were due to a new hormone in the extracts but soon found that all toxic substances—extracts of kidneys, spleen, and even toxicants not derived from living tissue—produced the same syndrome.

Selye surmised that the response to the injection of toxic substances reflected his “classroom concept” of “the syndrome of just being sick.” That is, adrenal enlargement, thymicolymphatic involution, and gastrointestinal ulcers were the omnipresent signs of damage to the body when under attack. The three changes thus became (for Selye) the objective indices of stress and the basis for the development of the entire stress concept.

First described in a note to *Nature* in 1936, GAS has three stages: alarm, resistance, and exhaustion. In the alarm stage, the body shows changes characteristic of the first exposure to the stressor; these changes generally coincide with the sympathetic discharge that enables the fight-or-flight phenomenon of Cannon. If the stressor continues and is compatible with adaptation, features of the alarm reaction disappear and resistance develops. Prolonged exposure to the stressor may result in exhaustion and finally death.

One of the most important findings of GAS is the stress-induced thymicolymphatic involution, which highlighted for the first time that stress has a major impact on the immune system. This concept preceded by more than 20 years the discoveries of lymphocyte recirculation by James Gowans and acquired immunological tolerance by MacFarlane Burnet and Peter Medawar. Selye’s discovery began the field of neuroimmunomodulation.

Selye soon became aware of the fact that the adrenal enlargement of GAS was associated with increased secretion of glucocorticoids (cortisol or corticosterone) that:

- Induce glycogenolysis, thereby supplying a readily available source of energy for the adaptive reactions necessary to meet the demands made by the stressors.
- Facilitate various other enzymatically regulated adaptive metabolic responses and suppress immune reactions as well as inflammation, assisting the body to coexist with potential pathogens.

Selye asserted that glucocorticoids are needed for adaptation to stress primarily during the alarm reaction. Selye's view that glucocorticoids enhance and mediate the stress response has been upheld with the additional concepts that glucocorticoids play a permissive role that primes the body's stress response systems and also prevent overshoot of the defense systems. Overshoots in the body's defense system are perhaps most dramatically seen in major inflammatory cataclysms called cytokine storms and the consequent systemic inflammatory response syndromes that play a key role in the lethality of avian influenza and have also occurred in response to the injection of certain antibodies. Exogenous synthetic glucocorticoids such as methylprednisolone remain a mainstay of the treatment of cytokine storms.

Although GAS is sometimes manifest in extreme stress, the three components of GAS have not withstood the test of time as indices of stress as Selye had originally proposed. Rather, the main biological markers of stress have long been behavioral observations and tests and measures of sympathetic and HPA activation. In the case of the latter, measurements of glucocorticoid concentrations in blood, either alone or in parallel with plasma concentrations of ACTH, have been used as the main biological indices of stress. So, despite its heuristic value, especially for stress-induced neuroimmunomodulation, the concept of GAS has lost scientific currency.

Stressors: Features of and Lack of Stressor Sign

In *Stress in Health and Disease*, Selye underscored the fact that:

Stress is part of our daily human experience, but it is associated with a great variety of essentially dissimilar problems, such as surgical trauma, burns, emotional arousal, mental or physical effort, fatigue, pain, fear, the need for concentration, the humiliation of frustration, the loss of blood, intoxication with drugs or environmental pollutants, or even the kind of unexpected success that requires an individual to reformulate his lifestyle.

Stress is present in the businessman under constant pressure; in the athlete straining to win a race; in the air-traffic controller who bears continuous responsibility for hundreds of lives; in the husband helplessly watching his wife's slow, painful death from cancer; in a race horse, its jockey, and the spectator who bets on them.

Selye went on to argue that "while all these subjects face quite different problems they respond with a stereotyped pattern of biochemical, functional, and structural changes essentially involved in coping with any type of increased demand upon vital activity, particularly adaptation to new situations."

Selye also asserted that stressors have no sign as far as evoking the stress response. That is, the response will be the same "whether the agent or situation being faced is pleasant or

unpleasant; all that counts is the intensity of the demand for readjustment or adaptation that it creates.” Selye underscored this point with the following poignant example:

The mother who is suddenly told that her only son died in battle suffers a terrible mental shock; if years later, it turns out that the news was false and the son unexpectedly walks into her room alive and well, she experiences extreme joy. The specific results of the two events, sorrow and joy, are completely different, in fact they are opposite to each other, yet their stressor effect—the nonspecific demand for readjustment to a new situation—is the same.

Nonspecificity of Stress Response

Selye seemed to have been driven to find specificity in the response to different types of stressors. Thus, again in *Stress in Health and Disease*, he wrote:

It is difficult to see at first how such essentially different things as cold, heat, drugs, hormones, sorrow, and joy could provoke an identical biologic reaction. Nevertheless this is the case; it can now be demonstrated by highly objective, quantitative biochemical and morphologic parameters that certain reactions are totally nonspecific and common to all types of agents, whatever their superimposed specific effects may be.

Criticism of Selye’s definition of stress has been put to experimental test. Pacak, Palkovits, and associates, for example, demonstrated that different stressors activate different stress biomarkers and different regions of the brain. Thus, low blood glucose concentrations (glucopenia) or hemorrhage activate both sympathetic and HPA systems; hyperthermia, cold, and formalin injection selectively activate the sympathetic system. On the basis of these data, Pacak and Palkovits conclude that each stressor has its own specific neurochemical signature. However, since these stress indices are limited to just two neurohumoral systems, and since for most stressors there is at least some overlap in response, it is not clear that this approach invalidates Selye’s definition, “stress is the nonspecific response of the body to any demand,” which would probably be unassailable had Selye omitted the term ‘nonspecific.’

Heat Shock (Stress) Proteins

Whatever the shortcomings of Selye’s definition of stress for the human, it is probably appropriate for the vast majority of living organisms. Living cells are classified into three main evolutionary lines or phylogenetic domains: Bacteria (eubacteria), Archaea (formerly archaebacteria), and Eucarya (eukaryotes, which encompass all plants and animals through to man). The cellular response to stress in all three phylogenetic domains is represented at the molecular level by the stress-induced synthesis of stress or Hsps, of which molecular chaperones and proteases represent two well-characterized families. The heat shock response was discovered in 1962 by Ritossa, who observed a pattern of *Drosophila* salivary gland chromosome puffs that were induced in response to transient exposure to elevated temperatures. Since then, many studies have shown that the heat shock response is ubiquitous and highly conserved in all organisms from bacteria to plants and animals. It is an essential defense mechanism for protection of cells from a wide range of stressors, including heat shock, alcohols, ischemia, inhibitors of energy metabolism, heavy metals, oxidative stress, fever, or inflammation, which depending on amplitude and duration can all cause cell death by apoptosis or necrosis. The heat shock response can protect against stress-induced cell death by way of a cell-protective process known as thermotolerance or cytoprotection, in which exposure of cells to mild stress conditions, sufficient to induce the expression and

accumulation of Hsps, protects against a subsequent challenge from another stress that is, by itself, lethal. Although their precise function remains to be determined, the high degree of conservation of these Hsps across species, coupled with their importance in cell survival in various conditions, suggests that Hsps are critical for both normal cellular function and survival after a stress. Several cytoprotective functions have been attributed to Hsps and, in particular, the HSP70 family. These include:

1. The folding of proteins in various intracellular compartments.
2. The maintenance of structural proteins.
3. The refolding of misfolded proteins.
4. Translocation of proteins across membranes and into various cellular compartments.
5. The prevention of protein aggregation.
6. The degradation of unstable proteins.

Hsps also serve as modulating signals for immune and inflammatory responses, and they may have a role in cytokine production.

So, for the heat shock response to stressful stimuli, Selye's "stress is the nonspecific response of the body [or cell] to any demand" would appear to be appropriate.

Concepts of Stress and Disease

There is a vast literature on the role or possible role of stress in the causation and/or exacerbation of disease in most organ systems of the body. Here, attention is focused on mental disorders. The *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* of the American Psychiatric Association recognizes two stress disorders: acute stress disorder and posttraumatic stress disorder (PTSD). For the diagnosis of acute stress disorder, the individual, while experiencing the trauma or after the event, must have at least three of several dissociative symptoms, such as a subjective sense of numbing, detachment, or absence of emotional responsiveness; reduction in awareness of surroundings; depersonalization; or dissociative amnesia. Following the trauma, the traumatic event is persistently reexperienced, the individual avoids stimuli that may arouse recollections of the traumatic event, and he or she has anxiety or increased arousal. The trauma causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

PTSD is defined as a condition in which a traumatic event is persistently reexperienced in the form of intrusive recollections, dreams, or dissociative flashback episodes. Cues to the event lead to distress and are avoided, and there are symptoms of increased arousal. To meet the diagnostic criteria of the DSM-IV, the full symptom picture must be present for more than 1 month, and the disturbance must cause clinically significant distress or impairment in social, occupational, or other areas of functioning.

PTSD has only been accepted officially as a mental disorder since 1980, when it was included, amid considerable controversy, in the DSM-III. References to the aftereffects of psychological trauma date back as far as the third century BC; achieved prominence during the early period of the railroad in Britain when rail travel, then precarious and physically traumatic, gave rise to a syndrome called railway spine or postconcussion syndrome; and were regarded as the basis for hysteria at the turn of the nineteenth century by neurologists and psychiatrists such as Jean-Martin Charcot, Pierre Janet, and Sigmund Freud. Long before

PTSD was included in any diagnostic system, Charles Dickens wrote *A Tale of Two Cities* (1859), which can be considered as an early case report of PTSD.

Interest in PTSD increased dramatically during World War I: Charles Samuel Myers was the first to coin the term and report case histories of 'shell shock,' which described a condition that afflicted many troops who screamed and wept uncontrollably, froze and could not move, became mute and unresponsive, and lost their memory, sensations, and capacity to feel. Pat Barker's monumental trilogy, *Regeneration*, deals poignantly with the psychological traumas of war and the nature of shell shock. The condition occurred again in vast numbers of people as a consequence of World War II. However, it was the psychological trauma experienced by Vietnam veterans and their demand for compensation that led to the inclusion of PTSD in the DSM-III as a condition that occurred both in civilian (e.g., rape trauma syndrome, battered woman syndrome, and abused child syndrome) and in military trauma response syndromes.

Future Developments of Stress Concepts

This brief account of some of the definitions and concepts of stress shows that there is still much to be done in the area of stress research. Thus, with respect to gene-environmental interactions, work on susceptibility genes has just begun, and there is still much room for expanding our knowledge about the role in stress of epigenetic factors and other mechanisms of gene control such as RNA interference. On the basis of previous experience, it seems likely that Barker's 'fetal origins' hypothesis might be honed and revised and may lead to a robust understanding of the metabolic syndrome and diabetes type 2. New powerful computer analysis of brain imaging and electrical recording may help to resolve the many questions that surround consciousness and cognition.

The vexed cause-and-effect questions regarding the influence of stress in mental disorders, cancer, and other diseases need to be answered. In the past 25 years, we have witnessed how Selye's cherished and widely accepted axiom that stress is the cause of gastric ulceration (one of the three components of GAS) was undone by the careful observations and courageous perseverance of Barry Marshall and Robin Warren, who demonstrated that, in fact, most gastroduodenal ulcers are caused by a microbe, *Helicobacter pylori*, that is readily amenable to treatment with antibiotics. And yet, there is evidence that stress does play a role in gastric ulceration, so the stress-H. pylori interaction needs to be worked out. These and other biological questions about stress are likely to be tractable—rational and rigorous biology will almost certainly win the day.

However, the causes of human stress, acute and posttraumatic, are commonly social and sociological, political and irrational (beliefs in religious and racial superiority). Our continuing strife and conflict reflect in part man's innate, often irrational (limbic-brain generated) drive for conquest, territory, acquisition, and reproduction of the species. Perhaps the fact that man is such a smart political animal works against us and could ultimately lead to our stressful self-destruction. It is not clear that anything can protect man from this fate.

See Also the Following Articles

- **Chronic (Repeated) Stress:** Consequences, Adaptations
 - **Corticotropin-Releasing Hormone:** Integration of Adaptive Responses to Stress
 - **Stress and Neuronal Plasticity**
 - **Stress and Parasympathetic Control**
 - **Stress:** Homeostasis, Rheostasis, Allostasis and Allostatic Load
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